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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SALMON, KATHERINE D	
ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/659,519	SIDRANSKY ET AL.	
	Examiner	Art Unit	
	KATHERINE SALMON	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 October 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12,15 and 19-24* is/are pending in the application.

4a) Of the above claim(s) *20-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12,15 and 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed 10/22/2008.

2. Claims 12, 15, 19-24 are pending. Claims 1-11, 13-14, 16-17 have been cancelled.

3. Claims 20-24 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 6/15/2006.

4. This application contains claims 20-24 drawn to an invention nonelected with traverse in the reply filed on 6/15/2006. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

5. The rejections presented below for claims 12, 15, and 19 are necessitated by amendment. Specifically the 35 USC 112/Enablement presented in the nonfinal (7/22/2008) has been altered as necessitated by amendments to the claims. Response to arguments follows.

6. This action is FINAL.

Claim Rejections - 35 USC § 112/ Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which

> it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 12, 15, and 19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

<u>The nature of the invention and breadth of claims</u>

Claim 12 is drawn to a method of detecting a cell proliferative disorder, comprising contacting a sample with RNA primers in exon 1 and exon 2 of the human p16 gene, amplifying the resulting extension product with a oligonucleotide which binds to a 5' ALT gene and determining the presence of a truncated p16 gene product with a homozygous deletion of exon 1, comprising detecting a first amplification product containing exon 2 of the p16 gene in the absence of identifying a second amplification product containing exon 1 of the p16 gene, wherein the presence of the truncated p16

gene product is associated with a cell proliferative disorder and wherein the cell proliferative disorder is lung or head and neck cancer. Claim 15 defines the sample. Claim 19 is defines the amplification reaction.

Therefore the claims encompass a method for detecting and correlating the absence of exon 1 of the p16 gene with lung or head and neck cancer in any sample type.

Nature of the Invention

The invention is in a class of invention, which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Guidance in the Specification

The specification asserts that the p16 gene has been identified as a region having homozygous deletions in many tumors and that the 5' ALT is shown to be about 30 kb upstream for p16 (p. 5 lines 6-9).

The claims are drawn to the detection of lung or head and neck cancer by detection the presence of a truncated p16 gene (e.g. the homozygous deletion of exon 1).

The specification asserts a method for detecting a cell proliferative disorder comprising contacting a cellular compound with a reagent which detects an alteration in p16 (p. 41 last paragraph). The specification asserts that the gene encoding the tumor suppressor p16 has been found to be deleted in certain cancers (p. 43 last paragraph).

The instant specification asserts a method of detecting the presence or absence of all or particular regions of the human chromosome 9p21 (p. 44 1st paragraph).

Working Examples

Example 1 part 1: The specification asserts cells from head and neck cancer cell lines, lung cancer cell lines, pancreatic adenocarcinomas cell lines were extracted (p. 47 last paragraph).

Example 1 part 2 and 3: The specification asserts fragments of exon 1, 2, and 3 were amplified (p. 48 and 49).

Example 4: The specification asserts the complete p16 and p16-5'ALT cDNA was amplified by RT-PCT (p. 57 1st full paragraph). The specification asserts that immunopreciptation was performed in which anti-p16 antibodies which recognize either the C-terminus or the N-terminus (p. 57 1st full paragraph). The specification asserts that the N-terminal antibody was not recognized indicating that the product lacked the N-terminal exon 1 coding sequence (p. 57 1st full paragraph).

Example 6: Table 1 presents 5' CpG island methylation related to allelic status and sequence analysis of the p16 in the cell lines. The p16 sequence indicates the majority of the primary human cancers, including head and neck and lung cancer, have the wild-type p16 sequence (p. 61). This indicates p16 with exon 1 present (wild type) would be observed in primary human cancers, therefore it is unpredictable to make an association of a mutant p16 gene (absent of exon 1) with cancers. Table 1 seems to indicate that NSCLC, SCLC, HNSCC had LOH of 9p21, however, the table is not clear because it also indicates that these tumors comprise the wild type p16 gene. Therefore

the Table is unclear with regard to rather it is showing that these tumors have a homozygous deletion of exon 1 or the presence of exon 1.

Example 8: The example asserts that none of the methylated cells lines of NSCLC, SCLC, and HNSCC expressed p16 (p. 63 1st full paragraph). However, this is not sufficient guidance for enablement purposes because the art (Zhang et al.) teach that observation in cell lines are not directly correlative to tumor samples.

Example 11: The specification asserts Exon 1 of p16 lies in a CpG island which is unmethylated in normal tissue (p. 67 1st full paragraph). Table 2 shows inactivation of p16 in cell lines and primary tumors (p. 69). Table 2 discloses that in cell lines only breast and renal cancer have homozygous deleted p16 exon1 genes (p. 69). Table 2 discloses that none of the primary tumors which include samples from breast, colon adenoma, and colon cancer have homozygous deleted p16 (p. 69). Therefore the specification discloses that in many samples such as primary tumors and some cell lines there is no correlation of cell proliferative disorder and the absence of exon 1 in the p16 gene product. This example does not discuss the cancer types the claims are currently amended and therefore does not provide guidance for the association of a homozygous deletion of exon 1 with detection of lung or head and neck cancer.

The unpredictability of the art and the state of the prior art

Zhang et al. (Cancer Research 1994 Vol. 54 p. 5050) teaches detection of homozygous deletions of the p16 gene in 68 primary head and neck squamous cell carcinomas and 9 head and neck cell carcinoma cell lines (Abstract). Zhang et al.

found that none of the primary tumors showed homozygous deletions of p16 (abstract). Zhang et al. teaches that p16 may play a role in tumorigenesis in some head and neck squamous cell carcinomas but it probably occurs more frequently in cell lines as a result to adaptation to cell culture (abstract). Therefore the art teaches that a correlation in cell lines is cannot be directly extrapolated to tumors in a patient.

Washimi et al. (Cancer Research 1995 Vol. 55 p. 514) teaches that the homozygous deletion of p16 was only observed in non-small cell lung cancer carriers and not in all lung cancer carriers (Abstract). Therefore the art teaches that not all types of lung cancer are correlative to homozygous deletion of p16.

Okamoto (Cancer Research 1995 Vol. 55 p. 1448) discloses the examination of p16 in primary lung cancer and metastatic lung cancers (abstract). Okamoto et al. teaches that alterations of the p16 gene were detected in 6 of the 22 metastatic non small cell lung cancers, but non were detected in 25 primary NSCLCs, 15 primary small cell lung cancers, or 9 metastatic sclcs (abstract). Okamoto et al. asserts that therefore p16 is a late event in NSCLC carcinogenesis (abstract). In contrast to Washimi et al., Okamoto et al. did not find a correlation in all non small cell lung cancers. As such, even in the art, the correlation between deletion of exon 1 and lung cancer is not predictable.

Quantity of Experimentation

The quantity of experimentation in this area would be extremely large since there is significant number of parameters that would have to be studied. To

practice the invention as broadly as it is claimed, the skilled artisan would have to determine the correlation of the deletion of exon 1 in the p16 gene with any lung or head and neck cancer wherein the art teaches that such associations are unpredictable.

Further the skilled artisan would need to perform undue experimentation to detect lung or head and neck cancer because both the art and the instant specification teach that deletion of exon 1 of p16 is not predictably detectable in all tumor or cell line types.

To use the invention as presented would require a large amount of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

Case law has established that '(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that '(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that '(I)t is the specification, not the knowledge of

one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement".

Thus the applicants have not provided sufficient guidance to enable a skilled artisan to make the claimed invention in a manner reasonably correlated with the claimed method of detection of lung or head and neck cancer. The skilled artisan would have to perform undue experimentation to determine correlation of the absence of exon 1 of the p16 gene because the art teaches that such correlations are unpredictable.

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the negative teachings in the art, and the lack of guidance provided in the specification balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Response to Arguments

The reply traverses the rejection. A summary of the arguments in the reply and response to arguments is presented below.

It is noted that the arguments made with respect to the analysis in the 35 USC 112/enablement rejection (7/22/2008) which have been removed from the 35 USC 112/enablement presented above are moot. The 35 USC 112/enablement rejection set forth above has been amended to reflect the amendments made in the instantly pending claims.

The reply asserts that the claims have been amended to lung cancer (examples 7 and 8) and head and neck cancer (examples 5 and 8) as therefore enabled by the instant specification (p. 4 4th paragraph).

These arguments have been fully reviewed but have not been found persuasive.

Though the claims have been amended to be limited to only the detection of lung or head and neck cancer, the claims as presented are still rejected over 35 USC 112/enablement because the instant specification has not provided sufficient guidance to make or use the method in light of the art of record. Specifically the reply points to the examples in the instant specification, however, as discussed above, none of the instant specification examples provide a statistically significant correlation between homozygous deletion of exon 1 and detection of lung or head and neck cancer. Further the art teaches that such associations are unpredictable. Zhang et al. teaches that correlations in cell lines are not predictive to correlations in primary tumors of head and neck cancer. Washimi et al. and Okamoto et al. both disclose that not all lunch cancers are correlative to a deletion of the p16 gene. As such the art teaches that such a direct correlation of these types of cancers and deletion of p16 is not predictive and as such the claims as amended have been rejected under 35 USC 112/Enablement.

Conclusion

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to KATHERINE SALMON whose telephone number is (571)272-3316. The examiner can normally be reached on Monday-Friday 8AM-530PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Katherine Salmon/
Examiner, Art Unit 1634

/Sarae Bausch/
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